REMARKS

Applicants acknowledge the time and courtesy accorded applicants by the Examiners, Ms. Bahar and Mr. Travers, at the Interview conducted July 14, 2003. The substance of the Interview is essentially reflected by the above amendments and following remarks.

The Amendments

The cancellation of lines 20-23 from page 2 eliminates possible confusion. Whereas the statements may have been correct as applied to the invention at the time it was first made (see the forthcoming inventorship correction documents), these do not apply to the state of the art as of the priority filing date. See in this regard the attached declaration filed by assignee in the re-issue application leading, for example, to re-issued patent RE 37,564.

The amendment to page 4 of the specification corrects an obvious typographical error. It would be self evident to one of ordinary skill in the art that the apparent reference to an absolute number of particles to define the particle size distribution is a typographical error. A skilled worker would immediately recognize that the correct units to define the particle size distribution would be a percentage of the particles, not an absolute number of particles. This is also clear from the correct usage of percentages when defining the particle size distribution for micronized estradiol at page 5, lines 5-9, of the instant specification. No new matter is added by the specification amendments.

Claims 1, 10, 18 and 44-49 are amended for clarity purposes to recite "oral" administration form as suggested by the Examiners at the Interview.

Claims 7, 9, 45, 47 and 49 are amended to be complete in describing the USP XXIII paddle method consistent with disclosure at page 4, lines 16-24, and Example 2, page 12.

Claims 9, 11, 38-40, 44, 46, 48 and 50 are further amended to correct obvious formal matters.

Claim 14 is amended to revert closer to the language of original claim 14 with some clarification as to the "number" term.

Claim 52 is amended to correct an obvious error; it was intended to correspond to original claim 4.

New dependent claims have been added which are clearly supported by the original disclosure; see, e.g., page 2, lines 32-33; page 4, lines 26-31; page 5, lines 18-24; page 9, lines 11-24; and Example 1.

New independent claims 57-60 are directed to kits having the ingredients as described for the existing claims but for a particular administration regimen supported by the disclosure of original claim 14 and the specification at page 7, line 34, to page 8, line 5, for example. New independent claims 66 and 67 are within claims 1 and 18 but recite more specific amounts of the actives.

The amendments do not narrow the scope of the claims.

The Rejection under 35 U.S.C. § 112, second paragraph, and related Objection

The rejection of claim 50 under 35 U.S.C. § 112, second paragraph, is believed to be rendered moot by the amendment thereto.

The rejection of claims 7, 9, 45 and 47-56 under 35 U.S.C. § 112, second paragraph, and the related objection to the specification and claims regarding the USP paddle method language are

respectfully traversed. These claims reciting the testing method have been amended so that they are consistent with each other and with the disclosure. The specification and claims all refer to the same standardized method for dissolution testing. This standardized testing method is in accordance with the USP ("United States Pharmacopeia, National Formulary") XXIII for dissolution testing of pharmaceuticals. Attached is a detailed description of the standardized method readily available to one of ordinary skill in the art. It makes clear what the method designates and what steps are involved. Thus, its recitation in the claims does not render the claims indefinite. Also, because the standard was well known in the art, applicants' reference to it is not an attempt to incorporate essential material by reference. Material which is well known in the art is not "essential." See, e.g., *Hybritech , Inc. v. Monoclonal Antibodies, Inc.,* 231 USPQ 81, 94 (Fed. Cir. 1986), stating a "patent need not teach, and preferably omits, that which is well known in the art.

Accordingly, it is urged that the rejection under 35 U.S.C. § 112, second paragraph, and the related objection to incorporation by reference be withdrawn.

The Rejections under 35 U.S.C. § 103

The rejections of the claims under 35 U.S.C. § 103, as being obvious over either Gast (WO 98/04269) or Gast (WO 98/04267) in view of Elliesen (U.S. Patent No. 5,922,349) are respectfully traversed. Because the issues are the same regarding both rejections, they will be discussed together.

In the prior Office Action of May 7, 2002, the prior art rejections for obviousness were based on the Gast references each alone. Although neither Gast reference teaches that the drospirenone

therein was micronized, it was stated that "one of ordinary skill in the art would have been motivated to employ known pharmaceutical actives in micronized form." But the rejections based on the Gast references alone were withdrawn. Elliesen is now cited because it is alleged to suggest the use of drospirenone in micronized form based on its disclosure at col. 10, lines 15-28.

As is believed to have been agreed during the above-mentioned Interview, one of ordinary skill in the art considering the Elliesen disclosure as a whole, would interpret the word "micronized" in the paragraph at issue to be modifying only the following word, "progesterone," and not the following listed synthetic progestogens, such as drospirenone.

The Elliesen passage in question (absent the parentheticals) recites:

> *Examples of progestogen which can be employed in this invention are micronized progesterone*
> *norethisterone acetate*
> *norgestrel*
> *levonorgestrel*
> *gestodene*
> *CPA*
> *chlormadinone acetat*
> *drospirorenone*
> *3-ketodesogestrel*

The most reasonable reading of this passage is that the word "micronized" modifies what follows it (i.e., only what immediately follows it, see discussion below), not the broader "progestogen" term preceding it. If the word "micronized" modified the general progestogen term preceding it, then, the thought being expressed is completed with the term "micronized" and the remainder of the current sentence (the named nine progestogens) simply dangles. Some intermediary punctuation and words would have been necessary to render the sentence sensible. But none exist.

The sentence, on the other hand, reads sensibly only if the term "micronized" modifies what follows it.

The next inquiry is whether the term "micronized" modifies only the immediately following term "progesterone," or all of the listed following synthetic progestogens. The original parent application from which the Elliesen patent derived (see attached page 17 of Ser. No. 08/535,402) recites the term "progesterone" directly after "micronized" without the return and has the following compounds separated by commas. This format made clear that "micronized" only applied to the "progesterone" term. This format was inadvertently modified when making other changes to this passage for filing of the CIP application which became the Elliesen patent. However, it is believed that a reading of the balance of the Elliesen patent in the context of one of ordinary skill in the art shows that the only reasonable interpretation is that "micronized" only applies to the progesterone term directly following it.

Immediately after the listing of the progestogens in col. 10 of Elliesen, there is an example of a preferred composition citing one of the preferred synthetic progestogens, i.e., levonorgestrel. The term "micronized" does not appear before the levonorgestrel term. If the micronized term in the paragraph in question was applicable to the listing of synthetic progestogens in addition to progesterone, it would be consistent that the recitation of levonorgestrel would be preceded by the term "micronized." But it is not. Similarly, claim 12 of Elliesen recites 3 synthetic progestogens but does not recite that they are micronized. Again, this is consistent with "micronized" being interpreted as only modifying the immediately following progesterone term. Further, claim 11 recites the preferred progestogens and recites them in the manner of the original parent specification

with the "micronized progesterone" term being together and being separated from the others by commas. Certainly, if the micronized term was to apply to the synthetic progestogens as well as progesterone, the term micronized would have appeared in the claims modifying the synthetic progestogen recitations. But, again, it does not. Further following this consistency, the synthetic progestogen used in the Examples 1-3 is not recited as micronized. Thus, the balance of the Elliesen disclosure makes the meaning of the passage at col. 10 of Elliesen clear – i.e., the only reasonable interpretation of Elliesen is that the "micronized" term applies only to progesterone and micronized drospirenone is not taught or suggested.

Additionally, attached is a copy of a declaration of Dr. Elliesen (an inventor of the Elliesen reference) submitted in related application Ser. No. 09/757,688. It addresses this same issue. He attests that the phrase "micronized progesterone" was a standard phrase used in the art because it was known that progesterone needed to be provided in micronized form or some other special form in order to be clinically relevant. The Lignieres (*Clinical Therapeutics* article) reference, of record herein, confirms that natural progesterone should be used in micronized form for adequate bioavailability. Thus, one of ordinary skill in the art would have understood that the use of "micronized" in Elliesen had a special connection with progesterone and would not be read as applying to the other progestogens, which are synthetic progestogens. Dr. Elliesen confirms that this was the understanding in writing the disclosure which became the Elliesen reference.

For these reasons, at least, Elliesen does not suggest the use of micronized drospirenone and therefore does not suggest modifying Gast in this manner. In the absence of such suggestion, the record fails to provide the requisite motivation to modify the prior art to meet the claim recitations.

The same reasons that the rejections over the Gast references alone were withdrawn apply because Elliesen does not cure the established deficiencies of the Gast references. Thus, both rejections under 35 U.S.C. § 103 should be withdrawn.

Clarifications

Clarifications of certain statements made in the response of January 14, 2002, are in order.

Being filed herewith is a copy of the package insert for the commercial oral contraceptive product corresponding to this application, i.e., Yasmin®. The drospirenone and ethinyl estradiol contained in these tablets are both micronized. The bottom of the middle column on page 963 mentions some of the same data reported in Example 4 of this application. Applicant's belief expressed throughout the specification and repeated in the first full paragraph on page 10 of the mentioned response, that micronized drospirenone has excellent bioavailability, is based on the data of Example 4, but not only thereon. However, as the Examiner has noted, Example 4 does not provide a comparison of micronized vs. non-micronized drospirenone.

Applicants are not relying on any unexpected advantage in establishing patentability because such a showing is unnecessary. The claims are not *prima facie* obvious. Whereas Example 4 does provide pertinent information concerning the invention, its description on page 10 of the prior response is inaccurate. In fact, in Example 4, two tablets containing 3 mg of drospirenone and 0.03 mg of ethinylestradiol were employed in a comparison with an oral suspension of 6 mg of drospirenone and 0.06 mg of ethinylestradiol. This would be eminently clear to a skilled worker. Otherwise, of course, the comparison would make little sense.

The specification, at page 4, lines 10-20, states that micronizing drospirenone, surprisingly, provides rapid dissolution *in vitro* (under the circumstances stated). The Declaration of Dr. Lipp (Paragraph 11) notes that, even if it had been expected that micronization would increase the exposure of oral drospirenone to the gastric environment, there still would have been no motivation to micronize drospirenone. However, pages 9 and 10 of the mentioned response are perhaps a little confusing in this regard.

The comments at the top of page 9 could be interpreted as implying that micronized drospirenone has an enhanced bioavailability compared to, e.g., non-micronized drospirenone. However, there is no evidence of record in this regard. But such evidence is not necessary to demonstrate patentability. The nonobviousness of the claims of this application is derived from the facts established in the Lipp Declaration. These show that no motivation existed for a skilled worker to arrive at any of the claimed subject matter, e.g., in view of the known acid isomerization of drospirenone to an inactive form. Thus, applicants are not relying on any unexpected advantage to establish the patentability of the claims, e.g., they are not relying on "enhanced bioavailability." Rather, applicants rely purely on the lack of requisite motivation to establish obviousness under the many cited Federal Circuit decisions of record. See, e.g., those in the first full paragraph of page 9 of the mentioned response.

Furthermore, the paragraph bridging pages 9 and 10 of the mentioned response addresses the situation which would have existed had there been a *prima facie* case of obviousness. As mentioned in the prior paragraph of that response, in order for a *prima facie* case of obviousness to exist, statements such as the following from the prior response would have been true: "Micronizing it

[drospirenone] would be expected to heighten the instability thereof;" and "the data shown in figures 1-3 confirms the expectation in the art that in a low pH environment, as would be found in the stomach, the micronized form of drospirenone dissolves more rapidly." In a vacuum, these statements appear to be inconsistent with applicants' position stated above, stated in the Lipp Declaration and stated in the specification. It is the absence of a *prima facie* case of obviousness, however, which accurately reflects applicants' position and not any possible contrary implications which might be derived from the paragraph bridging pages 9 and 10 of the mentioned response.

As for Example 5, its content is self-explanatory. Whether one of ordinary skill in the art could have expected the bioavailability and effectiveness shown therein is irrelevant for the reasons given above.

The undersigned apologize to the Examiners for any unintended, misdescription of these data in the response of January 14, 2002.

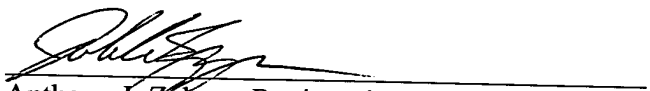
Inventorship and Information Disclosure

Assignee is currently re-investigating the inventorship of this application and expects to file a change of inventorship. Also, a supplemental information disclosure statement is filed herewith including facts concerning certain clinical studies. The fee in accordance with 37 C.F.R. §1.97(c) and 37 C.F.R. §1.17(p) is included in the payment.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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